Nuclear Magnetic Resonance Studies of 1,3-Butadienes. II. The Relation of (H,H) Coupling Constants to Conformation[1]

A. A. Bothner-By and R. K. Harris

Contribution from Mellon Institute, Pittsburgh, Pennsylvania 15213.
Received April 5, 1965

Values of (H,H) coupling constants for substituted 1,3-butadienes are summarized from the literature, together with the results of new measurements. These values are discussed in terms of σ- and π-contributions. The effects of conformation are considered in detail and the use of coupling constants for the conformational analysis of butadienes is established.

Introduction

A considerable quantity of scientific work has been directed to the determination of the conformation of 1,3-butadiene and its derivatives. A variety of physical methods has been used, including microwave,[2] infrared,[3] Raman,[4] and ultraviolet[5] spectroscopy, but until very recently little attention has been paid to n.m.r., partly due to the complexity of the spectra of butadiene and its simple derivatives. However, n.m.r. has proved extremely valuable in conformational assignments for other systems.[6] In particular the variation of vicinal (H,H) coupling constants with dihedral angle[7] has been extensively used for substituted ethanes and for cyclohexane derivatives. Recently, also, some long-range coupling constants have been shown to be highly stereospecific.[8] Measurement of the coupling constants for butadiene derivatives could be of great use for the assignment of conformation. Shortly after the commencement of this work, Hobgood and Goldstein[9] published accurate n.m.r. data for 1,3-butadiene and several derivatives and appended some comments on the significance of their results for conformational purposes. Apart from their paper, however, n.m.r. results for butadiene derivatives have occurred only sparsely in the literature, mostly as by-products of structural work. Moreover the compounds in question have often been rather complex, and the n.m.r. analyses of the spectra have frequently not been rigorous. Table I collates some of the data which seem most relevant to the purposes of this discussion. In addition, data for halogenated butadienes have been collected in Table I of the preceding paper of this series.[10]

It seems generally agreed that 1,3-butadiene itself and most of its simple derivatives exist principally in the planar s-trans conformation; butadiene itself has been said[11] to be at least 97% s-trans. However, several heavily substituted derivatives are probably not s-trans. In most of these cases it is not actually clear whether the stable conformation is s-cis or nonplanar. The main interaction which tends to destabilize the s-trans form for butadiene derivatives is that between substituents at positions 1 and 3 or 2 and 4 (Figure 1), this interaction being somewhat analogous to the well-known 1,3-diaxial interactions for cyclohexane derivatives. This explains, for instance, why the stable configuration of 1-substituted (or 1,4-disubstituted) butadienes is normally trans (or trans,trans; for example in 1,4-diphenyl-1,3-butadiene). The 1,3-interaction also accounts for the fact that neither 2,3-di-t-butyl-1,3-butadiene[12] nor hexachlorobutadiene[3-5] are s-trans. Bulky groups at position 3 (or 2) also destabilize the s-cis form due to an ethane-type eclipsed interaction so the two molecules mentioned above are actually nonplanar. In certain cases, when a substituent is highly electronegative (for example F or Cl) the 1,3-interaction may be attractive instead of repulsive. Thus Viehe has shown that the cis isomers of 1-chloro- and 1-fluoro-1,3-butadiene are more stable than the trans isomers.[13] Similar observations were also made for the 1,4-dichloro- and 1,4-difluoro-1,3-butadienes.[14] Such an attractive interaction may also be invoked to explain why the barriers to internal rotation about the central C–C bond for chloroprene and fluoroprene are substantially larger than that for 1,3-butadiene itself.[15]

Such factors must be considered in the attempt to characterize the conformation of 1,3-butadienes from a knowledge of coupling constants obtained from n.m.r. studies. It was intended first of all to obtain a series of coupling constants for molecules known to be or highly likely to be in the usual s-trans conformation and then to consider the values for molecules with large 1,3-interactions which might be supposed to exist in conformations other than the s-trans. In general, the measurements have been purposely limited to butadienes of labile conformation. Some interesting comparisons may, however, be made with coupling constants of molecules forced into a s-cis (or nearly s-cis) conformation by the presence of cyclic linkages (as in 1,3-cyclohexadiene). In this type of conforma-

(1) Based in part on a paper presented at the Symposium on Molecular Structure and Spectroscopy held at The Ohio State University, Columbus, Ohio, June 1964.
(2) D. Lide, Jr., *J. Chem. Phys.*, **37**, 2074 (1962).
(3) G. J. Szasz and N. Sheppard, *Trans. Faraday Soc.*, **49**, 358 (1953).
(4) K. W. F. Kohlrausch and H. Wittek, *Ber.*, **75**, 227 (1942).
(5) A. Roedig and R. Kloss, *Ann.*, **612**, 1 (1958); M. I. Batuev and A. D. Matveeva, *Zh. Obshch. Khim.*, **28**, 2903 (1958); *Izv. Akad. Nauk SSSR*, 1393 (1958).
(6) H. S. Gutowsky, *Pure Appl. Chem.*, 793 (1963).
(7) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(8) C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.*, **34**, 115 (1962).
(9) R. T. Hobgood and J. H. Goldstein, *J. Mol. Spectry.*, **12**, 76 (1964).
(10) A. A. Bothner-By and R. K. Harris, *J. Am. Chem. Soc.*, **87**, 3445 (1965).

(11) L. M. Sverdlov and E. N. Bolotina, *Russ. J. Phys. Chem. English Transl.*, **36**, 1502 (1962). Here, and in the succeeding text, the distinction between the configurational term *"trans"* and the conformational term *"s-trans"* should be borne in mind.
(12) H. Wynberg, A. de Groot, and D. W. Davies, *Tetrahedron Letters*, 1083 (1963).
(13) H. G. Viehe, *Chem. Ber.*, **97**, 598 (1964).
(14) H. G. Viehe and E. Franchimont, *ibid.*, **97**, 602 (1964).
(15) W. G. Fateley, R. K. Harris, F. A. Miller, and R. E. Witkowski, *Spectrochim. Acta*, **21**, 231 (1965).

Table I. Coupling Constants[a] for Some 1,3-Butadiene Derivatives

Compd.	^2J	^3J_c	^3J_t	^3J_s	^4J_c	^4J_t	$^5J_{tt}$	$^5J_{cc}$	$^5J_{tc}$	Ref.
1,3 Butadiene	1.74	10.17	17.05	10.41	−0.83	−0.86	1.30	0.69	0.60	9
2-t-Butyl-1,3-butadiene (2 ≡ CMe₃)	2.30 (4,4') 1.70 (1,1')	10.80	17.00	...	±0.40[b]	±1.00[b]	0.00	0.00	0.00(1,4') 0.00 (1',4)	9
2,3-Di-t-butyl-1,3-butadiene (2,3 ≡ CMe₃)	1.51	...	...	...	...	...	<0.4	<0.4	<0.4	12
2-Methoxy-1,3-butadiene (2 ≡ OCH₃)	(−1.90) (1,1') 1.87 (4,4')	10.82	17.27	...	0.00	0.00	1.50	0.51	0.57 (1,4') 0.51 (1',4)	9
2,3-Dimethoxy-1,3-butadiene (2,3 ≡ OCH₃)	−2.21	...	...	...	...	...	1.51	0.56	0.90	...
cis-cis-Dimethyl muconate (1,4 ≡ CO₂CH₃)	...	11.8	...	11.3	...	−1.3	±1.3	...	...	30
cis-trans-Dimethyl muconate (1,4' ≡ CO₂CH₃)	...	10.7	14.8	10.7	?	0.0	...	...	0.0	30
trans,trans-Dimethyl muconate (1',4' ≡ CO₂CH₃)	...	...	16.5[c]	11.2[c]	−0.7	...	...	±0.6	...	30
trans,trans-Muconic acid (1', 4' ≡ CO₂H)	...	...	15.79	(11.7)	−0.71	...	...	(0.5)	...	31
cis-Tagetone (3 ≡ CH₃; 4' ≡ CO·CH₂CHMe₂)	1.34	10.86	17.73	...	±0.55	...	...	±1.59	±0.59	31
trans,trans-1,4-Diphenyl-1,3-butadiene (1', 4' ≡ Ph)	...	...	15.62	10.80	−0.94	...	...	0.90	...	...
Cyclohexadiene	...	+9.42	...	5.14	...	+1.06	+0.91	...	...	28

[a] In c.p.s.   [b] Magnitudes may be interchanged; signs unknown.   [c] Assignment has been reversed.

tional analysis considerable use may be made of theoretical expectations for coupling constants. Such theory will therefore be dealt with in a later section.

Experimental

Materials. The sample of 2,3-dimethoxy-1,3-butadiene was obtained through the kind offices of Dr. R. Hirst. *trans*-1,4-Diphenyl-1,3-butadiene was purchased from Matheson Coleman and Bell.

Spectra. Proton n.m.r. spectra were obtained as outlined in the preceding paper.[10]

Analysis of the Spectra

The n.m.r. spectra of several halogenated butadienes studied in the present work have been discussed in the preceding paper.[10] Given here for the first time (Table I) are the n.m.r. parameters for two further butadiene derivatives, *trans,trans*-1,4-diphenyl-1,3-butadiene (in
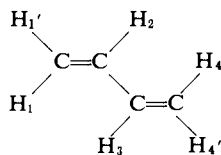
Figure 1.

solution in CCl₄) and 2,3-dimethoxy-1,3-butadiene (neat liquid). The diene protons of both compounds give rise to spectra of the AA'BB' type. Moreover in both cases the lines are broader than normal single lines. In the case of *trans,trans*-1,4-diphenyl-1,3-butadiene the broadening is probably due to slight coupling of the diene protons to protons of the aromatic rings; in the case of 2,3-dimethoxy-1,3-butadiene there is presumably slight coupling to the methyl protons. For the latter compound the high-field group of lines was distinctly broader than the low-field lines, and the spectral analysis was performed using mainly the spacings within the low-field group.

The parameters for 2-methoxy-1,3-butadiene published by Hobgood and Goldstein,[9] were used as trial values for the calculation of the spectrum of the dimethoxy compound. The calculations were performed as described in the previous paper, using the iterative computer program[16] LAOCOON II. For the AA'BB' nuclear magnetic system it is not, of course, possible to assign the chemical shifts unambiguously. For the diphenyl compound the values τ 3.164 and 3.429 were obtained. Comparison with the values for butadiene itself and for styrene,[17] *trans*-propenylbenzene,[18] and propene[19] indicates that the protons with the low-field shift are those at the 1- and 4-positions. Both chemical shifts are well to low field of those for butadiene itself,[9] and it is therefore probable that the stable form of the molecule is that in which the phenyl rings are coplanar with the butadiene skeleton (and the diene protons are therefore in the plane of the phenyl rings). This, of course, gives the maximum opportunity for delocalization of the π-electrons. The τ-values for the diene protons of 2,3-dimethoxy-1,3-butadiene were not measured accurately but the mean value was τ 5.64 and the internal chemical shift was 35.81 c.p.s.

The low-field group of lines was assigned to the 1- and 4-protons in accord with the shifts reported for methyl vinyl ether[17] and 2-methoxybutadiene,[9] as well as the low-field shift observed for the 1-proton in chloroprene.[3] If this is the case, the relative breadths of the lines shows that long-range coupling through five bonds from the methyl protons of a methoxy group is stronger to the *cis* proton of the neighboring vinyl group than to the *trans* proton.

Mechanism of Long-Range Coupling

It has proved to be convenient to consider two possible mechanisms for long-range, spin–spin coupling be-

(16) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, 41, 3863 (1964).
(17) C. N. Banwell and N. Sheppard, *Mol. Phys.*, 3, 351 (1960).
(18) R. W. Fessenden and J. S. Waugh, *J. Chem. Phys.*, 30, 944 (1959).
(19) A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, 83, 231 (1961).

tween protons, namely, coupling occurring through the σ-bond electronic framework, and that through the π-bond system.[20] The latter involves σ–π configuration interaction in the neighborhood of each of the coupled protons. These mechanisms will be referred to here as σ-coupling and π-coupling, respectively, although it is not clear how far these can actually be treated independently. Theoretically[20] π-coupling gives rise to positive coupling constants when the protons are separated by an odd number of bonds, and negative coupling constants when an even number of bonds intervene. This has also been stated to be true for σ-coupling on the Dirac vector model,[8] but a somewhat simplified molecular orbital approach[21] (using a mean energy for electronic excitation) indicates that σ-coupling should always be positive, and the present position is thus somewhat confused. In a recent paper Koide and Duval[22] have pointed out that one expects a positive sign if the dominant σ-mechanism is that of overlap of the proton orbitals but an alternation in sign if the dominant mechanism is a chain of interatomic and intraatomic couplings (analogous to the Dirac vector model). Naturally the former mechanism will only hold for specific stereochemical relationships. Experimentally the sign alternation for π-coupling has been verified,[20] but both positive and negative ^4J-values have been reported for σ-coupling.[23] From its positive sign the ^4J meta coupling in benzene derivatives has been assumed to be due to σ-coupling.[8]

Normally, σ-coupling falls off very rapidly with increasing separation of the coupled protons; it is usually <1 c.p.s. when there are four intervening chemical bonds and negligibly small for larger separations. However, anomalously large, long-range coupling constants have been observed in cases where the intervening bonds are in the so-called "straight-zigzag" conformation[8] (Figure 2) in which all the atoms in the coupling chain are in the same plane. This effect has been attributed without a great deal of proof to σ-coupling, and we shall refer to it as anomalous σ-coupling. At any rate it is evident that σ-coupling is very sensitive to conformation (as in the case of ethanic vicinal coupling constants[7]). Frequently the anomalously high values are associated with the fact that one or more of the intervening carbon atoms is sp² hybridized.[24]

By contrast π-coupling does not fall off so rapidly as the number of intervening bonds increases. Karplus[20] distinguishes two mechanisms for π-coupling, one involving correlation of the spin of a proton with a π-electron sited on an adjacent carbon atom and the other involving correlation with a π-electron sited on a carbon atom two bonds removed. We refer to these mechanisms by the terms vinylic and allylic coupling, respectively, although again it is not clear that they can in fact be distinguished. Karplus[20] calculated the contributions to coupling constants from these two mechanisms by relating them to hyperfine splitting constants and triplet state energies for related free radicals. The magnitude of the allylic coupling de-

Figure 2. Straightest zigzag conformations.

pends on the dihedral angle between the C–H bond and the adjacent double or triple bond. It is zero when that angle is zero, that is when the nodal plane of the π-bond contains the allylic proton. The magnitude of the vinylic and allylic couplings are independent of configuration, that is they are the same for cis and for trans coupling paths across double bonds. The extent of π-coupling depends clearly on the delocalization of electrons among the bonds separating the coupled protons. For a true double bond the attenuation of the coupling should be negligible. When there are two equivalent paths for π-coupling, as for triple bonds, the effect should be approximately doubled. Karplus[20] calculated that the π-contribution to ^3J was ≈1.5 c.p.s. for an ethylenic compound and ≈4.6 c.p.s. for acetylene. Karplus[20] himself did not consider the effect for a conjugated series of formally single and multiple bonds, but in the acetylenic series, measurements by Snyder and Roberts[25] showed that the increase of a conjugated chain by one —C≡C— group attentuates the coupling between the end protons by a factor of about 2. If this is true in the ethylenic series also, then π-coupling through five bonds should be approximately 0.7 c.p.s. According to the above ideas, therefore, in butadiene the π-contributions to $^5J_{cc}$, $^5J_{ct}$, and $^5J_{tt}$ should be equal, ≈0.7 c.p.s. in magnitude and positive in sign, while the π-contributions to ^4J_c and ^4J_t should also be equal, and should be only slightly greater than the contributions to ^5J (say ≈0.8 c.p.s. in magnitude) and negative in sign.

Long-Range Coupling Constants for 1,3-Butadiene

The experimental values for butadiene[10] (see Table I) show that predictions based on π-coupling alone, as outlined in the last section, are sufficient to account for all the observed values except $^5J_{tt}$. It can be seen that whereas $^5J_{cc}$ and $^5J_{tc}$ are equal to within experimental error, $^5J_{tt}$ has about twice their magnitude. It is interesting to note that the trans,trans protons are separated by a zigzag chain of bonds in precisely the manner presumed empirically to be necessary for anomalous σ-coupling.[8] The zigzag condition is not fulfilled for $^5J_{cc}$ or $^5J_{tc}$ nor for either of the ^4J couplings. The latter are equal within experimental error and are negative in sign. We therefore propose that for 1,3-butadiene the π-mechanism gives rise to the coupling constants ^4J_t, ^4J_c, $^5J_{cc}$, and $^5J_{tc}$, but that π- and anomalous σ-mechanisms are of roughly equal importance for $^5J_{tt}$. Coupling constants have also been reported for vinyl acetylene,[26] and these fall into the same pattern. For this molecule ^5J_t = 0.85 c.p.s. and ^5J_c = 0.7 c.p.s. The somewhat larger value for ^5J_t may indicate a contribution from the anomalous σ-effect since the geometry is somewhat similar to the zigzag requirement (the coupled C–H bonds are parallel). The value of ^4J is higher (2.1

(20) M. Karplus, J. Chem. Phys., 33, 1842 (1960).
(21) H. M. McConnell, ibid., 24, 460 (1956).
(22) S. Koide and E. Duval, ibid., 41, 315 (1964).
(23) A. A. Bothner-By and C. Naar-Colin, J. Am. Chem. Soc., 84, 743 (1962); F. A. L. Anet, ibid., 84, 747 (1962); E. W. Garbisch, Chem. Ind. (London), 1715 (1964).
(24) S. Sternhell, Rev. Pure Appl. Chem., 14, 15 (1964).

(25) E. I. Snyder and J. D. Roberts, J. Am. Chem. Soc., 84, 1582 (1962).
(26) E. I. Snyder, L. J. Altman, and J. D. Roberts, ibid., 84, 2004 (1962).

c.p.s.) than for butadiene since there is an allylic contribution using the π-bond with a nodal plane perpendicular to the plane of the molecule, with the optimum allylic dihedral angle of 90°.

The Effect of Conformation

In the above discussion, it is assumed that butadiene exists in the *s-trans* conformation. It is obviously of great interest to ask what contributions to long-range coupling would exist for other conformations. If long-range σ-coupling is only significant when the bond path between the protons in question is in the extended zigzag form, then all nonplanar conformations of butadiene derivatives will have zero contributions to coupling from σ-mechanisms. However, the *s-cis* conformation will have a σ-contribution to ^4J_t (of questionable sign, but probably positive), but no such contribution to $^5J_{tt}$. Long-range vinylic π-coupling will only occur when the molecule is planar and thus conjugated, but there will be an allylic contribution to ^4J for nonplanar conformations (a maximum for 90° rotation from planarity), but not for the *s-cis* conformation. It is not anticipated that π-contributions to coupling in the *s-cis* conformation will significantly differ from those in the *s-trans* conformation.

Therefore from the above discussion it might be predicted for a molecule existing entirely in the *s-cis* conformation $^5J_{tt} \approx {}^5J_{cc} \approx {}^5J_{tc} \approx +0.7$ c.p.s., $^4J_c \approx -0.8$ c.p.s., with the value of ^4J_t uncertain. A nonplanar 1,3-butadiene derivative, on the other hand, would be expected to have ^5J-coupling constants all reduced in magnitude below the *s-trans* values, presumably approaching zero if there is substantial departure from planarity. The magnitude of the ^4J-coupling constants should not be affected so much, however, and in particular will probably not be negligible in any circumstances. If the ^4J-value for vinylacetylene[20] is considered to be composed of vinylic and allylic mechanisms, with the former of the same magnitude as in butadiene, the allylic contribution to ^4J would be expected to be ≈ -1.2 c.p.s. at the most.

Long-Range Coupling Constants for Butadiene Derivatives

The discussion of the previous section must be borne in mind while the values of Table I (and of Table I of the previous paper[10]) are considered. Naturally, there will be specific substituent effects on the coupling constants superimposed on any conformational effects. It would seem that substitution at the interior positions with a highly electronegative atom or group reduces the magnitudes of ^4J_c and ^4J_t, the latter rather more than the former. For fluoroprene the value of ^4J_t actually becomes positive in sign, although the magnitude is not much greater than the experimental error. We believe that similar electronegativity effects[27] are the cause of the zero values reported for ^4J_c and ^4J_t in 2-methoxybutadiene by Hobgood and Goldstein.[10] Similarly it is probable that specific substituent effects are responsible for the increase in magnitude of ^4J_t by about 0.3 c.p.s. and the decrease of ^4J_c by about 0.1 c.p.s. for the 1,4-dichlorobutadienes from the values for 1,3-butadiene itself.

The values recently obtained by Manatt[28] for 1,3-cyclohexadiene are very important for our purposes. Cyclohexadiene may not be exactly planar, but it must be quite close to the *s-cis* form. It may be seen that in accordance with the discussion in the previous section the magnitude of $^5J_{tt}$ is much less than the value for butadiene although it is still significantly larger than the values for $^5J_{cc}$ and $^5J_{tc}$ in the latter molecule. It is possible that there is a residual contribution from the anomalous σ-mechanism to $^5J_{tt}$ in cyclohexadiene since although the coupling path is not of the zigzag type the C–H bonds of the coupled protons are parallel (in fact they are linear) as is the case for vinylacetylene discussed previously. Of greater significance, however, is the fact that ^4J_t is positive for 1,3-cyclohexadiene. This would indicate a large ($+1.9$ c.p.s.) contribution from the anomalous σ-mechanism which more than compensates for the negative π-contribution. Due to the presence of the bulky *t*-butyl group, 2-*t*-butylbutadiene is probably nonplanar.[9] The values of ^4J_c and ^4J_t are therefore of great interest. Unfortunately it is not possible in this case to unambiguously assign the resonances of the 1- and 1′-protons, nor is it possible to determine the signs of ^4J_c and ^4J_t. Arguments based on chemical shifts would indicate a reversal of the assignments given by Hobgood and Goldstein.[9] It is necessary to find a better model nonplanar butadiene for these studies.

As Hobgood and Goldstein[9] have pointed out, the negligibly small values for the ^5J-coupling constants in 2-*t*-butylbutadiene are probably due to the nonplanarity of the molecule, which annihilates any π-contribution. It would appear that the coupling constants over five bonds are also very small for 2,3-di-*t*-butylbutadiene,[12] as would be expected, since the line widths[29] are less than 0.4 c.p.s. The results for ^4J and ^5J in *cis,trans*-dimethyl muconate[30] are not sufficiently well documented for any useful comment to be made on their anomalous magnitudes at this stage.

It would appear that in general the ^5J-coupling constants should be of more use than the ^4J-values for detecting whether butadiene derivatives exist in nonplanar conformations, both because $^5J_{tt}$, $^5J_{cc}$, and $^5J_{tc}$ all seem to become vanishingly small as planarity is lost, and because many common butadiene derivatives, being 2,3-disubstituted, have no ^4J-coupling constants. However the change in sign of ^4J_t in passing from an *s-trans* to a *s-cis* conformation may well be the best means of detecting the latter by n.m.r. The ^4J-values seem to be more sensitive to specific substituent effects.

The Values of ^3J_s for Butadiene Derivatives

Vicinal coupling constants have proved of such great use in conformation studies of saturated compounds, because of the dependence on dihedral angle, that it may be asked why they have not been considered at length here. The reason is simply that a great limitation is imposed by the absence of ^3J_s for any butadiene derivatives substituted at the 2- and/or 3-position, such derivatives being common. In particular those molecules which are probably nonplanar (2-*t*-butyl-

(27) H. Booth, *Tetrahedron Letters*, 411 (1965).

(28) S. L. Manatt, to be published.
(29) We are grateful to Dr. Wynberg for showing us his original spectrum.
(30) J. A. Elvidge and L. M. Jackman, *Proc. Chem. Soc.*, 89 (1959).

butadiene,[9] 2,3-di-*t*-butylbutadiene[12]) all lack ^3J_s. However in other cases the use of ^3J_s can be powerful, as is shown by the difference between the values for butadiene[9] (10.41 c.p.s.) with a dihedral H–C–C–H angle of 180° and 1,3-cyclohexadiene[27] (5.14 c.p.s.) which has a dihedral angle probably within 20° of zero. The ratio of the two values is 2.0 compared to the ratio of 1.1 calculated by Karplus[7] for ethane and the observed ratio of 1.6 for ethylene.[24] The discrepancy may be indicative of the nonplanarity of cyclohexadiene.

These studies, including the data previously published in the literature,[31] have established the values of

(31) E. O. Bishop and J. I. Musher *Mol. Phys.*, 6, 621 (1963).

coupling constants to be expected for the *s-trans* conformation of butadiene derivatives and have indicated (and partly substantiated) the probable values for other conformations. The use of n.m.r. coupling constants has been shown to be a potentially powerful tool for determining the conformation of such molecules. Work is in hand with the aim of obtaining more definite values (including signs) for molecules known to exist or likely to exist in the nonplanar or *s-cis* conformations. Work initiated on 1,1,3-trichlorobutadiene and analogous compounds will be reported at a later date.

The Synthesis and Nuclear Magnetic Resonance Spectra of Epimeric 16-Deuterio-17β- and -17α-estradiols[1]

Jack Fishman

Contribution from the Institute for Steroid Research, Montefiore Hospital, New York 67, New York. Received February 15, 1965

The synthesis of the 16α- and 16β-deuterio derivatives of 17β- and 17α-estradiol is described. The n.m.r. spectra of the four isomeric structures, with particular reference to the C-17 proton resonance, are discussed. The n.m.r. data permit the drawing of certain conclusions as to the conformation of the steroidal ring D bearing a C-17 hydroxyl substituent.

The synthesis of 17β- and 17α-estradiols stereospecifically labeled at C-16 with deuterium was required in order to study further the conformation of ring D by means of n.m.r. Until now the only n.m.r. data available for a complete series of C-16, C-17 substituted isomers involved carbomethoxy and acetyl substituents.[2] The steric bulk and chemical and electronegative nature of these groups gives rise to interactions which affect the n.m.r. data to such an extent that the values reported can be considered to be specific only for a particular series. The deuterated compounds reported in this paper are particularly suitable for the study of C-17 proton resonance in ring D. The deuterium substitution at C-16 simplifies the ABX pattern of the 17-proton to the AX which permits a more precise analysis of the H-16, H-17 coupling constants. At the same time the size of the isotope does not lead to steric distortion of ring D.[3] Furthermore the chemical and electronegative character of the substituent is essentially indistinguishable from hydrogen so that complications from these factors are avoided. The aromatic ring A is another advantage, since the chemical shift of the 17-proton is now unique in

the molecule. The deuterated series could be used as a standard with which n.m.r. studies of otherwise substituted D-ring may be compared. The knowledge obtained may permit the application of n.m.r. to the difficult problem of ring-D conformation.

The synthetic sequences developed with these compounds where the orientation of the isotope can be demonstrated by physical means should then be applicable to reactions in which tritium is the isotope desired. These radioactive compounds would then be available for the study of biochemical pathways of the metabolism of the female sex hormone, with certainty that the isotope was in the correct position in the molecule.

In order to ensure stereospecificity, the synthesis of both the 16α- and 16β-deuterated compounds was achieved by two alternative stereoselective procedures. Introduction of the deuterium in the 16β-position was effected by the following methods. The readily available 16α-hydroxyestrone (Ia)[4] was converted to the ditosylate Ib which was then reduced with LiAlD₄. This reduction proceeds with inversion[5] to give the 16β,17α-dideuterio-17β-estradiol (IIa). The latter was converted to the 3-monobenzoate IIc and oxidized with the Jones reagent[6] to give 16β-deuterioestrone benzoate (IIIa) which was reduced with LiAlH₄ to give the desired 16β-deuterio-17β-estradiol (IVa). A second sequence was LiAlD₄ reduction of the 16α,-17α-epoxide V[7] to give 16β-deuterio-17α-estradiol (VIa). The phenolic group was protected as the benzoate VIc and oxidation of the 17α-hydroxy group with the Jones reagent[5] proceeded without loss of

(1) This work was supported by a grant from the American Cancer Society and a research grant (CA 07304-1) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) A. D. Cross and P. Crabbe, *J. Am. Chem. Soc.*, 86, 1221 (1964).

(3) See, for instance, A. D. Cross and C. Beard, *ibid.*, 86, 5317 (1964).

(4) W. R. Biggerstaff and T. F. Gallagher, *J. Org. Chem.*, 22, 1220 (1957).

(5) G. K. Helmkamp and B. F. Rickborn, *ibid.*, 22, 479 (1957).

(6) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

(7) V. Prelog, L. Ruzicka, and P. Wieland, *Helv. Chim. Acta*, 28, 250 (1945).